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REMARKS

I. Status of the Claims

Claims 1-24 were canceled in a preliminary amendment. Claims 25-27 are currently pending under examination.

II. Amendment to the Specification

The specification is amended to provide updated priority information as well as to provide a brief description of Figure 5. No new matter is introduced.

III. Claim Rejection

35 U.S.C. §103(a)

Claims 25-27 were rejected under 35 U.S.C. §103(a) for alleged obviousness. Specifically, the Examiner asserted that the claims are obvious over U.S. Patent No. 5,099,005 (the '005 patent) in view of Kim *et al.*, U.S. Patent No. 6,358,710 (the '710 patent), Pierce Product Information for ImmunoPure IgG1 Fab and $F(ab')_2$ preparation kit (Pierce Product Information), and U.S. Patent No. 4,281,061 (the '061 patent). Applicants respectfully traverse the rejection.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

The present invention relates to a kit for making $F(ab')_2$ fragments from a glycosylated antibody comprising a hinge region. The hinge region contains one or more protease cleavage sites and has one or more adjacent non-hinge regions, which contain one or more attached oligosaccharide groups. The oligosaccharide group(s) cause the protease cleavage site(s) within the hinge region to be resistant to a protease treatment. There are at least two components in the claimed kit: first, a deglycosylation composition comprising at least one glycosidase capable of catalyzing the hydrolysis of an N-glycosidic or O-glycosidic linkage

between a sugar unit and an amino acid to form a partially or wholly deglycosylated antibody; and, second, a protease composition comprising one or more proteases capable of reacting with said partially or wholly deglycosylated antibody to produce said $F(ab')_2$ fragments from said partially or wholly deglycosylated antibody.

In contrast, the cited references teach the following: the '005 patent relates to methods of enhancing immunoglobulin fragment yield, which include the step of desialylating the immunoglobulin; the Kim *et al.* reference reports the observation of O-linked glycosylation in the hinge region of mouse IgG2b, which the authors believe renders the hinge region resistant to proteolysis of the heavy chain; the '710 patent describes humanized NR-LU-13 antibodies and discusses the possible modification of the antibody's glycosylation status; the Pierce Product Information provides description of a kit for preparing IgG1 Fab or $F(ab')_2$, which contains proteases and instructions but no enzyme for deglycosylation; and the '061 patent does not directly relates to the elements of the pending claims and is cited, according to the Examiner, to show that "components or reagents can be provided as kits as a matter of convenience, optimization and economy of the users" (page 4, lines 1-2, of the Office Action mailed June 23, 2006).

Applicants first contend that the cited references fail to provide all limitations of the pending claims. For instance, the pending claims recite that the glycosylated antibody contains one or more ***non-hinge regions that are adjacent to the hinge region*** and have one or more attached oligosaccharide groups, which cause the hinge region to resist proteolysis. The removal of the oligosaccharide group(s) is achieved by at least one glycosidase hydrolyzing an N-glycosidic or O-glycosidic linkage between a sugar unit and an amino acid. The cited references do not provide this limitation, since the '005 patent does not describe the hydrolysis of the N- or O-glycosidic linkage between a sugar unit and an amino acid, the Kim reference describes O-glycosylation ***within the hinge region***, and the '710 patent makes no distinction in the specific location within an immunoglobulin where glycosylation or its modification may take place, whereas the Pierce Product Information and the '061 patent bear no relevance to deglycosylation at all.

Secondly, even assuming that all claim limitations can be found in the above cited references, the Examiner still has not established that these references, when viewed together, provide a suggestion or motivation to combine the claim limitations. Quite to the contrary, the '005 patent in fact explicitly teaches away from the present invention. As already discussed in Applicants' previous response (filed January 23, 2006), the '005 patent not only fails to teach the use of an N-glycosidase and/or an O-glycosidase to break the N- or O-glycosidic linkage between a sugar and an amino acid in order to facilitate the production of $F(ab')_2$, but also specifically states that ***antibodies should be treated with a sialidase only*** to remove the terminal sialyl residues of the antibody oligosaccharides. This feature of desialylation is repeatedly emphasized as an essential component of the invention. See, *e.g.*, column 2, lines 40-52, column 5, lines 26-28, and Abstract.

On the other hand, what the Examiner has relied on as the motivation to combine is merely the reasoning that, since Kim teaches O-glycosylation in the hinge region renders the region resistant to proteolysis, and the '710 patent teaches deglycosylation by N-glycosidase or O-glycanase (columns 19-20), it would therefore be obvious for a skilled artisan to substitute desialylation by sialidase with deglycosylation by glycosidase. Applicants cannot agree with the Examiner, because this reasoning does not take into consideration two important factors: one, the explicit teaching away by the '005 patent as indicated above; and two, the non-specific nature of the discussion offered by the '710 patent regarding antibody glycosylation. A closer review of the paragraph bridging columns 19 and 20 of the '710 patent reveals that this is merely a generic description of what types of glycosylation may exist in an immunoglobulin and how the glycosylation status can be modified (such as by glycosidase treatment). This description reflects nothing more than the general knowledge in the field of protein glycosylation and presents nothing specific for an antibody molecule or the production of its fragments. As such, the Kim reference and the '710 patent together do not provide a specific suggestion or motivation to substitute the desialylation of antibodies with deglycosylation of antibodies for the purpose of producing $F(ab')_2$ fragments. This is true even without considering the explicit teaching away by the '005 patent.

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As the Federal Circuit has emphasized in numerous occasions, the obviousness determination must be made when the claimed invention is considered as a whole, the references are considered as a whole, and the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. See, *e.g.*, *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187n5 (Fed. Cir. 1986), and MPEP §2141 II. Applicants contend that, when all evidence, particularly the explicit teaching away from the present invention by the '005 patent, is considered together, the conclusion of obviousness is untenable.

In summary, no showing of *prima facie* obviousness has been made. The withdrawal of the obviousness rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Chuan Gao
Reg. No. 54,111

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
CG:cg
60854757 v1